CARCINOMA OF THE PANCREAS.

EXPLORATORY OPERATION; STUDY OF THE FAT ABSORPTION.

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Clinical History by Dr. Northrup.

There are two features of especial interest in this case, viz., the diagnosis of the character of the disease and the location of the lesion in the head of the pancreas. The history is as follows:

The patient's father died of "cancer of the throat." His personal history is that of an exceptionally healthy, robust, enduring man of large physique, ruddy; in short, a man having all the physical features of an ideal coachman. A better glimpse of his regular life, temperance, and habits cannot be given than to state the fact that from early manhood to the time of his death he had never been out of employment, and had been coachman in all that time to but three families, two of them being Governors-General of Canada, the third a United States Senator.

The patient was forty-six years old and married. When first taken sick he weighed 220 pounds. His first symptom was pain in the back. Exposure while sitting upon the box in bad weather was set down as the cause of his illness, and he was allowed to send the second coachman when the weather was unfavorable. The rheumatism of the back grew no better, but he again forced himself to do full duty as driver. The pain at length grew so much worse that he could not endure long waits, and sought professional advice for the increasing rheumatism of the back. The first course of treatment given him was potassium iodide in increasing doses, with the application of the cautery along the skin of the dorso-lumbar region. This afforded temporary relief, but soon it became evident that the pains were growing more unbearable and interfered with sleep. They seemed worse at night. After a short sleep in the evening and early night the pains were such that he was obliged to sit up, taking "cat naps," as he expressed it.

In May, five months after his first pains, the patient entered the hospital for a week to allow study of his case, to the end that a diagnosis might be made. At that time it appeared that his bowels were somewhat inclined to constipation, that he experienced flatulence, eructations, and occasional vomiting an hour after eating. It also appeared that he had lost about forty pounds. This he attributed to the disturbance of his stomach due to taking so much medicine (potassium ?), to loss of appetite and loss of sleep. His maximum weight had been 220 pounds, and his theory of the cause of loss was thought reasonable. Lavage relieved the eructations, but the pain continued, as did insomnia. A test-meal followed by Günzberg's test showed a good reaction—free hydrochloric acid. The urine was normal, and physical examination revealed nothing abnormal.

No diagnosis was recorded, but it is fair to the observers of this case to state that during this visit to the hospital the conjecture was expressed that this man would continue to lose flesh and would reappear with cancer of the stomach.

After leaving the hospital he was to continue daily lavage. For a time he had success in self-treatment—no more vomiting, only occasional lumbar pains, and persistent insomnia.

After another month, six months or more from the appearance of the first pains in the back, diarrhœa began—five or six loose movements daily —which continued to the end of life.

In the tenth month of illness (from first pains) he returned to the hospital, having lost seventy pounds, his complexion bearing the stamp of cachexia. Günzberg's test showed a faint reaction. Nothing could be felt in the epigastrium, though the abdominal walls were relaxed and depressed. Under chloroform a tumor was at once felt. It was just above the umbilicus, almost in the middle line, perhaps a little to the right, slightly movable—*i. e.*, it could be dragged a little to the right, so that the aorta could be felt pulsating at its left. The tumor did not move with respiration; was believed to be not connected with the greater curvature of the stomach, but distinctly coinciding in position with the head of the pancreas. As felt through the relaxed abdominal wall, it seemed like a cricket-ball—*i. e.*, round, sharply circumscribed, elongated.

The diagnosis of carcinoma of the head of the pancreas was made, and the patient transferred to the surgical division for exploratory operation. It may here be stated that the number and character of the passages of the patient (five to six loose motions daily) recalled to the mind of the writer some observations long since heard, that the diagnosis of pancreatic disease is sometimes aided by studying the stools. One observer claimed to have found fat floating on the stools, etc. With this thought in mind, without knowing whence it came, whether from reliable English observers (to the best of recollection) or from most unreliable sources, a systematic observation of the passages was instituted. The nurses reported that the passages were quite unusual in appearance, being gray stone-color, soft, pasty, and that accompanying them was a brownish watery fluid, like water with a little molasses dissolved in it, or like thin, brownish machine oil. Upon the surface was thought to be an oily film. These appearances varied but little, though occasionally a pulpy emulsified appearance was described. Whatever value these points should subsequently reveal, the diagnosis accompanying the patient to his operation was carcinoma involving the head of the pancreas and occluding the duct.

The reasons for considering (1) the lesion cancer were cachexia and emaciation (loss of weight, seventy pounds); and (2) the lesion not of gastric origin, were the presence of free hydrochloric acid in the gastric contents, also the further fact that the tumor did not feel freely movable; and (3) for considering the tumor a pancreatic involvement, the fact of its location, that the mass was scarcely movable, swaying a little to the right, not moving with respiration; that the soft, pasty, gray diarrhœal passages seemed to contain an excess of fat.

Exploratory operation was performed by Dr. McCosh, who described the findings as follows: A mass shaped like a very thick "pancake," involving the head or middle portion of the pancreas, including so many vessels that removal was out of the question.

The patient was returned to the medical division, when his wound had healed, for study of the fat absorption. He continued to have passages of the same appearance as before, three to five daily.

At this point we were fortunate in interesting Dr. C. A. Herter in the case, and securing his services in a careful study of the total intake and outgo of fats.

About one year from his first described pains in the back our patient was transferred to his home, an hour by train. He rapidly failed, and a month later died. Every effort to secure an autopsy failed, and the question whether the tumor occluded the pancreatic duct alone, or occluded both the pancreatic and biliary ducts, will never be answered.[1] By so much it falls short of being a classical case. The complete history of the case, then, accentuates the "second feature of especial interest in this case, viz., the locating of the disease in the head of the pancreas."

Chemical Examination of Feces and Urine by Dr. Herter.

The appearance of the stools from the patient who presented the foregoing history, having been such as to indicate the presence of a more than usual quantity of fat, it was thought desirable to make a study of the fat absorption in his case, in the hope that it might throw some light upon the relation of the retroperitoneal tumor (which was discovered under chloroform and subsequently verified by operation) to the patency of the pancreatic and biliary ducts. The chief object of the investigation was to determine how large a proportion of the fat introduced with the food was absorbed from the gastro-enteric tract, and how large a proportion was lost with the feces, it being known that the absorption of fats is apt to be greatly reduced when the pancreas is the seat of extensive disease, or when the pancreatic duct is impervious, or when the bile ducts are obstructed. The period of observation extended over seven days. During this time the patient was upon an exclusive milk diet. An accurate record was kept of the quantity of milk taken each day. A representative portion of each day's milk was set aside for the determination of the fat-content. The following table shows the facts relating to the quantity of milk and fat received daily:

Date.	Grammes of milk ingested.	Per cent. of fat, *i. e.*, ethereal extract.	Grammes of fat ingested daily.
October 29	2580	4.25	109.1
" 30	2850	3.49	90.0
" 31	2640	5.30	139.9
November 1	2640	4.45	117.5
" 2	3120	5.23	163.2
" 3	8240	4.41 (estimated)	142.9
" 4	3240	3.74	121.2
Total milk	20,040	Average 4.41	Total fat 883.8

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[1] It is of interest that about ten weeks after the date of this study the patient developed intense jaundice, which lasted until his death, one week later. The appearance of jaundice probably corresponds to the implication of the common bile duct by the neoplasm.

It is thus seen that the patient received 883.8 grammes of fat in the seven days of the experiment, or 126.3 grammes daily—a generous but not extreme daily allowance of fat.

During a period corresponding to the seven days in which the fat-content of the milk was determined, the total quantity of feces was saved, with a view to ascertaining, first, the quantity of fat lost by the feces during the seven-day period, and, second, the relative proportion of neutral fats, fatty acids, and soaps. Owing to an oversight, an exact separation (by charcoal) of the feces corresponding to seven-day period was not effected. The period during which the feces were saved began and ended just twenty four hours later than the period during which the food was studied. An error is thus introduced, but it is probably very small, as the diet of the patient previous to the time of the study had for some time been essentially the same as that of the seven-day period. In order to prevent the action of micro-organisms in further splitting the neutral fat into fatty acids and glycerin, the feces were placed in a saturated solution of bichloride of mercury immediately after they were passed. As first passed the feces were typical acholic movements, light gray in color, and of the consistence of a soft pomade. Microscopical examination showed numerous fatty acid crystals. The epithelial detritus was not bile-stained. The feces were studied chemically, not in one portion from the entire week's collection, but in three separate portions. The percentage results given here represent averages obtained from the three portions. The total ethereal extract of the feces for the seven days was 335.36 grammes. The total ethereal extract from the milk taken during the period was, as above stated, 883.8 grammes. The fats soluble in ether which were lost by the feces thus amount to 37.95 per cent. of the fats introduced with the milk.[1] The ethereal extract of the feces does not, however, represent the total fat of the feces. The neutral fat of the feces and its fatty acids are extracted by ether, but the soaps do not enter into solution. It was, therefore, necessary to determine the fat present in the form of soaps in the residue of the feces (after extraction by ether). This was done by decomposing the soaps, liberating their fatty acids and extracting these by means of ether. A not inconsiderable quantity of fat was recovered in this way. Thus, the total fats of the feces, including fatty acids, neutral fats, and soaps, amounted to 415.11 grammes. This is equivalent to 46.76 per cent. of the fat ingested as milk. This loss of fat in the feces is greatly in excess of that which normally occurs. Thus, Mueller[2] in three healthy adult individuals found that the percentage of fat lost by the feces was 7.2 per cent., 16.9 per cent., 10.5 per cent. Of the known causes of a largely excessive loss of fat by the feces—*i. e.*, of defective fat absorption—there are two which may be excluded in this case: First, the excessive ingestion of fat, and, second, the presence of diarrhœa.[1] There are, however, two other causes of markedly reduced fat absorption which have to be considered carefully in reference to our patient—the absence of the pancreatic juice and the absence of the bile. In his study of the feces in jaundice, Mueller found that where the bile was wholly absent from the intestine the proportion of ingested fat that reappeared with the feces varied from 55.2 to 78.5 per cent. In several of Mueller's cases it was learned by autopsy that the bile was shut off from the duodenum owing to mechanical conditions, while in the same cases the pancreas was normal in appearance and its duct pervious. These cases constitute proof that the absence of bile may be the cause of greatly decreased fat absorption. This conclusion is in perfect accord with the experimental observation of Munk, who found in dogs with biliary fistula that the fat absorption was much reduced. Whether there are ever any exceptions to this influence of the bile on fat absorption we have yet to learn.

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[1] The ethereal extract of the feces constituted 49.98 per cent. (or three portions) of the dry substance of the feces. The following percentages of fat were obtained from normal feces from different individuals: 19.98, 26.39, 11.55, 17.90, 19.95, 12.58, 13.78, 21.39, 15 32, 14.17, 16.66, and 26.55 per cent.

[2] Untersuchungen über Icterus, Zeitschrift für klinische Medicin, Bd. 12, 1887, p. 45. This is probably the most important work on fat absorption hitherto published.

The influence of the pancreatic juice on the absorption of fats is less well understood and observations are more conflicting. Walker found that the stools were clay-colored or stone-colored and fatty in two cases of diabetes in which there was no jaundice, and in which autopsy showed disease of the pancreas, but no alterations in the liver. The stools were not studied chemically in these cases. In support of the view that fat stools may result from absence of the pancreatic juice is the evidence derived from the extirpation experiments of Abelmann,[2] of Minkowski,[3] and especially of Harley.[4] These observers found a marked reduction in fat absorption after extirpation of the pancreas. Harley obtained the striking result that the fat lost by the feces equalled or even exceeded that introduced when the pancreas had been removed from dogs.[5] In opposition to these findings are those obtained by Hartsen and by Mueller. Hartsen,[6] in two diabetics with extreme atrophy of the pancreas, found no increase in the fat of the stools, though from eight to ten spoonfuls of cod-liver oil were part of the day's food. Mueller could observe no distinct increase in the fat lost by the stools in two cases of pancreatic disease (one of advanced atrophy of the pancreas, another of cystic degeneration), though the food contained a usual quantity of fat. There are also numerous experimental results in opposition to those obtained, as mentioned above, by Abelmann, Minkowski, and Harley. Whatever conclusions may ultimately be reached as the result of new observations upon the relation between the pancreatic juice and fat absorption, it seems clear that extensive pancreatic disease does not *necessarily* interfere with the absorption of fat. So far, therefore, as our case is concerned, we cannot feel sure that the reduced fat absorption is due exclusively to disease of the pancreas, although we know from the exploratory laparotomy that the head of the pancreas was extensively diseased. We are unable to say whether the defective fat absorption depends on shutting out of the pancreatic juice alone or on the absence of both bile and pancreatic juice.

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[1] In a patient suffering from acute intestinal indigestion, with repeated large pale movements, I found that the feces contained 53.91 per cent. of ethereal extract on one occasion, and 56.43 per cent. on another. The fat content returned to normal after three days.

[2] Inaug. Dissert. Dorpat, 1890.

[3] Zur Lehre von der Fettresorption, Berlin. klin. Woch., 1890, p. 833.

[4] The Journal of Physiology, vol. xviii., 1895.

[5] The excess of fat is attributed to the presence of fat in degenerated epithelium from the gut-

[6] Quoted by Nothnagel, Erkrankungen des Darms, 1895, p. 21.

The careful studies of Mueller indicate that the pancreatic juice possesses the power of splitting the higher neutral fats into glycerin and the corresponding fatty acids. Neither the gastric juice nor the bile appears to possess this property. It was found by Mueller that in three cases of pancreatic disease the neutral fat in the stools was markedly increased—in one case it was 50.83 per cent., in another 52.3 per cent., and in a third 77.57 per cent. It seems probable that we may interpret habitual deficient fat-splitting as an indication that the pancreatic juice is deficient. In our own case the fat of the feces upon analysis yielded the following results:

	Second portion of feces.	Third portion of feces.	Average of three portions of feces.
Neutral fat . . .	17.87 per ct.	20.53 per ct.	17.50 per ct.
Fatty acids . . .	64.73 "	62.12 "	64.92 "
Soaps	17.70 "	17.35 "	17.58 "

In the three normal patients previously mentioned the neutral fats amounted to 27.88, 20.5, and 24.8 per cent. of the total fat of the feces. I have obtained similar percentages in a number of stools from normal persons.

It is thus evident that the breaking up of the neutral fats was accomplished as fully as in health. How is this to be explained on the assumption that the pancreas is the seat of extensive disease? Although we know that exclusion of the pancreatic juice from the intestine *may* occasion diminished splitting of neutral fat, there is no doubt that the breaking up of neutral fat into fatty acids and glycerin may be brought about to a considerable degree by the activity of micro-organisms. Thus, Escherich found in infants that the colon bacillus is capable of exerting such an action. In our case we have positive evidence that the bacterial activity of the intestine was more pronounced than is usual in health. Thus, it was found that the ethereal sulphates of the urine, which constitute a rough index of the extent of putrefaction of proteid substances in the intestine, were considerably increased. On October 30th the ethereal sulphates amounted to 0.484 gramme. The proportion of the ethereal or combined sulphates to the preformed sulphates on this day was 1 : 5.19. In health, on a milk diet the quantity of the ethereal sulphates in the twenty-four hours' urine from a man of average weight is generally less than 0.250 gramme. The proportion of the ethereal to the preformed sulphates (which is a more reliable index than the absolute quantity) varies from 1 : 15 to 1 : 25 on a milk diet. Again, in our case the indigo-blue of the urine, as tested by Obermeyer's solution, gave an exceptionally strong reaction on October 30th, such as is never seen in health and seldom in disease. The quantity of the indoxyl compound, the oxidation of which is the cause of the indigo-blue reaction, was shown to be unusually great in the urine collected during three of the seven days. The phenol contained in a twenty-four hours' urine amounted to 0.083 grammes. This is considerably in excess of what should be found in a patient on a milk diet, and is another indication of excessive putrefaction in the intestine. These observations collectively can only be interpreted as showing that for some reason the putrefaction of proteids in the intestine was excessive. We know through the increased indigo-blue yielded by the urine that the production of indol was excessive in our patient's intestine. I believe I have demonstrated that the chief cause of the indol production in the intestine is the activity of the common colon bacillus.[1] If, as stated by Escherich, the colon bacillus is capable of splitting fats, we seem fully justified in regarding bacterial activity as a factor in the fat splitting in the case of our patient, and it is probable that this influence is capable of fully compensating any deficiency in the fat-splitting ferment of the pancreatic juice.

It has been claimed by Pisenti,[2] that one of the consequences of shutting out the pancreatic juice from the intestine is the diminution of that proteolysis which leads ultimately to production of indol as well as other aromatic products, and to a consequent reduction of the indican of the urine. It is, however, now well understood that indol is one of the products of proteid putrefaction under the activity of the colon bacillus, and the strong indican reaction observed in the urine of our patient cannot be interpreted as inconsistent with the view that the pancreatic juice does not reach the gut.

One other feature of the feces of our patient calls for comment—the apparent absence of coloring matter. The absence of the color indicative of transformed bile pigment has usually been regarded as evidence that the bile has not entered the duodenum. Walker,[1] however, claims that light or stone-colored stools may arise as the result of pancreatic disease when the liver ducts are not implicated, and mentions two cases which seem to support the view that the pancreatic juice is as essential to the yellow or brown color of the stools as is the bile. We can hardly regard as settled the significance of stools which apparently contain no yellow or brown pigment, and it is somewhat surprising that so few accurate observations exist with reference to so important a subject. It is, however, clear, in the light of Walker's observations, that we are not safe in concluding that the bile is shut off from the duodenum simply because the stools are apparently acholic.[2]

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[1] On Certain Relations between Bacterial Activity in the Intestine and the Indican of the Urine. British Medical Journal, October, 1897.

[2] Ueber den Zusammenhang zwischen der Einwirkung des Pancreas auf die Eiweisskūken und die Indicanmenge in Urine. Arch. per le Scienze med., 1887, vol. xii., No. 5.

To sum up, the study of our patient while on a milk diet shows (1) that a decidedly excessive quantity of the ingested fat was lost with the feces; in other words, that fat absorption was distinctly impaired; (2) that the fat-splitting process was accomplished as fully as in health, and (3) that the putrefaction of proteids in the intestine was excessive. The persistence of these conditions in themselves constitutes evidence that either the pancreatic juice or the bile, or both, were wholly or partially excluded from the intestine. An exploratory laparotomy showed that the pancreas was the seat of malignant disease. Therefore we may regard the condition mentioned as due to pancreatic disease rather than to disease of the liver or bile ducts, but we have no proof that the bile ducts were not also implicated, and that the bile as well as the pancreatic juice was deficient in the intestine. The fact that there was no glycosuria is not inconsistent with extreme pancreatic disease, nor was the presence of a large amount of indican in the urine. It is possible that an autopsy would have thrown additional light on the cause of the deficient fat absorption, but it must be remembered that the conditions as regards the patency of the pancreatic and bile ducts might be quickly altered by a rapidly growing neoplasm.

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[1] On the Clinical Significance of Colorless or Clay-colored Stools Unaccompanied by Jaundice, etc. Medico-Chirurgical Transactions, London, 1889, vol. lxxii. p 257.

[2] Quincke, in an instructive paper (Münchener med. Wochenschrift, 1896, p. 854) calls attention to the fact that gray-colored stools, apparently acholic, may persist for weeks, urobilin being in reality present, as can be shown by extracting the feces with acidulated alcohol. The evidence favors the view that the feces sometimes contain a chromogen derived from hydrobilirubin, which is coexistent with an acholic appearance of the stools. Unfortunately, there are as yet no observations on the fat-content of the stools under these conditions. -

ON THE PRESENCE OF NEUSSER'S PERINUCLEAR BASOPHILIC GRANULES IN THE BLOOD,

AND THEIR RELATION TO THE ELIMINATION OF THE ALLOXURIC BODIES IN THE URINE.

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The observation, originally made by Neusser,[1] that under certain conditions granules may be found in the blood, which manifest a marked affinity for basic dyes and are located in immediate contact with the nuclei of leucocytes, has received comparatively little attention. This is the more surprising in view of Neusser's claim that these granules are essentially found in patients the subjects of the uric-acid diathesis, and may be regarded as pathognomonic of the disease in the widest sense of the term, viz., including gout, lithiasis, muscular rheumatism, nervous asthma, skin affections, gastro-intestinal derangements, diabetes, leucæmia, neuralgia, and neurasthenia. The only exception to this rule was noted in certain tubercular subjects, in which the granules were at times found, and which Neusser believed pursued a more favorable course than those in which the granules were absent.

Kolisch, a pupil of Neusser's, likewise regards these granules as evidence of the uric-acid diathesis.[2] But, while Neusser believes the diathesis in question to be associated with an increased elimination of uric-acid, Kolisch finds the uric acid relatively diminished, but the xanthin-bases actually increased to such an extent that the alloxuric bodies as a whole are eliminated in increased amount.

The text-books on clinical diagnosis which have since appeared make little mention of the subject. v. Jaksch[3] thus merely states that further observations will show to what extent Neusser's basophilic granules are of diagnostic interest. Cabot[4] likewise brings nothing new. The only other observations upon the subject which I have been able to find recorded in the literature come from Futcher and Fisch, in this country.

Futcher's results, however, in no way bear out the correctness of Neusser's view, and he concludes his most valuable report as follows: These observations do not in any way confirm the theory that there is a regular coincidence between an abundance of the granules and an increased excretion of the alloxuric bodies, nor do they favor the view that Neusser's granules occur exclusively in patients with an alloxuric diathesis. Cases occur in which, with numerous granules in the leuco-

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[1] Neusser. Wiener klin. Wochen., 1894, vii. p. 71.

[2] Kolisch. Ibid., 1895, viii. p. 797.

[3] Clinical Diagnosis. Fourth edition.

[4] Clinical Examination of the Blood. Wm. Wood & Co., New York, 1897.